

## REMARKS

In the present Office Action, the Examiner rejects claims 1-12, 13-20 under 35 U.S.C. 101 and 112, 2<sup>nd</sup> paragraph as being improper process claims and for failing to particularly point out and distinctly claim the subject matter of the invention. In response, the Applicant notes that a Preliminary Amendment was filed in the present case but not considered by the Examiner. The Preliminary Amendment cancelled claims 1-20 and replaced them with claims 21-31. The Applicant has attached a copy of the Preliminary Amendment, with the filing receipt, for the Examiner's review. The documents are attached as Exhibits A and B, respectively. Applicant believes that the new claims in the Preliminary Amendment traverse the Examiner's rejections as discussed below.

### *Claim Rejections – 35 U.S.C. § 101*

The new claims are directed to a medicament and not a process. As such, the Examiner's § 101 rejection that the process claims recite only a use is believed to be moot.

### *Claim Rejections - 35 U.S.C. § 112, 2<sup>nd</sup> paragraph*

With regard to the Examiner's rejection of claim 1 for containing "to an individual of a human being or an animal," the Applicant has cancelled claim 1. None of the new claims contain this language. Likewise, claims 13-20 have been cancelled and the Examiner's rejection regarding the amount of nicotine compound in these claims has been overcome.

### CONCLUSION

Applicant believes that it has overcome the Examiner's rejections and that pending claims 21-31 are now allowable.

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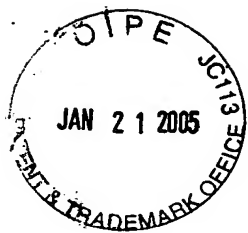
Respectfully submitted,

By



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of )  
László Bense )  
on USE OF AT LEAST ONE SUBSTANCE )  
BASED ON NICOTINE AND/OR A )  
SUBSTANCE PRODUCED FROM SAID... )  
Serial No.: National Stage Entry of )  
Int'l Appln. No. : PCT/SE00/01683 )  
International Filing Date: 1 September 2000 )  
Filed: Simultaneously herewith ) (Our Docket No. 6783-01WOUS)

Hartford, Connecticut, March 1, 2002

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PRELIMINARY AMENDMENT

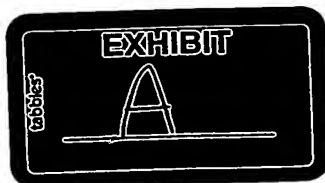
SIR:

Prior to examination on the merits, please amend the above-identified  
application as follows:

In the Specification:

Page 1

Please insert after the Title the following paragraph:



### Cross-Reference to Related Applications:

This application is entitled to the benefit of and incorporates by reference essential subject matter disclosed in International Patent Application No. PCT/SE00/01683, International Filing Date September 1, 2000; Swedish Application No. 9903085-0, filed on 1 September 1999; and Swedish Application No. 0001075-1, filed on 27 March 2000.

Please replace the first paragraph with the following paragraph:

The present invention refers to a use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to human beings or animals. The invention also refers to a method for prophylactic or therapeutic treatment of obstructive lung diseases in human beings or animals.

Please replace the last paragraph that begins on page 1 and ends on page 2, with the following paragraph:

During normal inhalation the bronchi are expanded, which counteracts the obstruction to a certain extent. During the following exhalation the lung tissue is compressed, including the bronchi, and a somewhat smaller gas volume may therefore flow through the respiratory tract. This leads to a valve effect when a certain balance arises. By a certain overpressure in the respiratory tracts and the lung, the obstruction may be overcome and the inhaled gas volume be emptied. The pressure in the lung is however not sufficient for completely emptying the lung. There is always a certain amount of air (residual volume; normally about 500 ml of an adult) in the lung after the first breath. This balance depends inter alia on and is influenced by the ambient air pressure; the greater the pressure the weaker the respiratory tracts, especially for early born, immature children.

## Page 2

Please replace the second paragraph with the following paragraph:

During smoking the mucous membrane in the respiratory tracts and bronchi is irritated, which leads to a swelling of the mucous membrane. This swelling decreases the lumen of the respiratory tracts, i.e. the obstruction arises and thus the air flow in the respiratory tracts is restrained. This leads to an increase in valve effect, resulting in a higher pressure in the respiratory tracts and the lung, and to a larger residual volume in the lung. The increase also leads to a destruction of tissue, which further reduces the gas exchange, i.e. the breathing capacity. If nicotine or nicotine-like substances are supplied, not via the respiration, a vessel contracting, decongestant effect, which reduces the obstruction, is obtained.

Please replace the third paragraph which begins on page 2 and ends on page 3, with the following paragraph:

Pulmonary barotrauma appears from tissue destruction caused by the above-described inner pressure. Pulmonary barotrauma may principally refer to one single alveolus or a smallest respiratory tract, or several small alveoli within the lung. If this tissue destruction process is expanded to the whole lung it is called pulmonary emphysema. In the cases when air is collected diffusely in the lung tissue proper, we have an interstitial emphysema or in a delimited way, a bulla (blister). If the air is collected adjacent to the pleura in a delimited manner we have a subpleural bleb. The air may also come to the intrapulmonary space and we have a so-called pneumomediastinum or into the heart sack; pneumopericardium. If the tissue destruction is expanded so that the pleura is destroyed, we have a spontaneous pneumothorax (SP). With regard to the fact that pathophysiological changes in the lung are documented in case of SP, it is not any longer relevant to call SP a disease of the pleura.

## Page 3

Please replace the first full paragraph with the following paragraph:

The obstruction leads to an expansion in one part of a lung and thus compression in the surrounding remaining portion of the lung. Such an expansion and compression is irreversible for a smoker even if he would stop smoking. If the surrounding compressed lung part is very large, surgery could be considered for removing a large significant blister and thus create space for the respiratory work. However, it is very rare that a patient is suitable for such an operation, whereby an expected effect is far from being optimal.

#### Page 4

Please replace the second, third and fourth full paragraphs with the following paragraphs:

This object is obtained by the use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to human beings or animals for the purpose of counteracting or preventive lung diseases in a prophylactic or therapeutic manner.

The applicant has realised that nicotine, if it is not supplied via the respiration, has an inhibitory effect on the development of respiratory tract obstruction followed by the irreversible substance loss, elasticity loss and expansion of the lung tissue, i.e. the negative effects arising from pulmonary emphysema, pulmonary barotrauma and spontaneous pneumothorax. By supplying nicotine to the body of the persons suffering from pulmonary emphysema, it is possible to prevent or limit the development of the disease. Nicotine also ought to have a prophylactic effect, i.e. the origin of pulmonary emphysema of persons having a risk to be effected by this disease, for instance smokers, which have stopped smoking, may be prevented by the supply of nicotine, however not via the bronchi, respiratory organs.

The definition of at least one substance based on nicotine and/or a substance produced from said one substance is to be given a broad interpretation and in this definition are included substantially pure nicotine, nicotine compounds, nicotine related compounds, nicotine derivatives, intermediate metabolites of nicotine and/or nicotine compounds, degradation products from

nicotine or nicotine compounds with completely or partly identical, similar effects.

Page 6

Please replace the second paragraph with the following paragraph:

The object is also obtained by a method for prophylactic or therapeutic treatment of obstructive lung diseases of human beings or animals, wherein said individual is supplied with a nicotine-based substance.

In the claims:

Please cancel all of the claims of the application, namely claims 1-20, and add the following new claims 21-31:

21. (New) A medicament for counteracting obstructive lung disease comprising a therapeutically effective amount of at least one substance based on nicotine and a pharmaceutically acceptable carrier, adjuvant or diluent.

22. (New) The medicament according to claim 1 wherein the therapeutically effective amount of at least one nicotine based substance is supplied via the blood path.

23. (New) The medicament according to claim 1 wherein the therapeutically effective amount of at least one nicotine based substance is administered via the gastrointestinal tract.

24. (New) The medicament according to claim 1 wherein the therapeutically effective amount of at least one nicotine based substance is administered transdermally.

25. (New) The medicament according to claim 1 wherein the therapeutically effective amount of at least one nicotine based substance is administered intravascularly.

26. (New) The medicament according to claim 1 wherein the therapeutically effective amount of at least one nicotine based substance is administered intranasally.

27. (New) The medicament according to claim 1 wherein the therapeutically effective amount of at least one nicotine based substance is administered intravaginally.

28. (New) The medicament according to claim 1 wherein the at least one nicotine based substance includes substantially pure nicotine.

29. (New) The medicament according to claim 1 wherein the at least one nicotine based substance includes nicotine derivatives, intermediate metabolite of nicotine, or degradation products of nicotine.

30. (New) The medicament according to claim 1 wherein the at least one nicotine based substance is absorbed by a binding agent.

31. (New) The medicament according to claim 1 wherein the therapeutically effective amount of at least one nicotine based substance is administered to a mammal having a congenital bilateral bronchial anomaly.

#### REMARKS

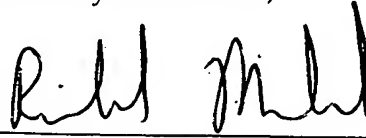
The above amendments are being made to place the application in better form for prosecution, to include the amended claims of the International Application, and to remove multiple dependencies from its claims.

Should the Examiner have any questions regarding the present application, Applicant respectfully requests that the Examiner contact Applicants' representative at the phone number listed below. While Applicant believes no

fees are due with the filing of this amendment, please charge any deficiencies in fees associated with this filing to our Deposit Account No. 13-0235.

Respectfully submitted,

By

A handwritten signature in black ink, appearing to read "Richard R. Michaud", written over a horizontal line.

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- 5 Use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament, and a method for treatment of obstructive lung diseases

10 THE BACKGROUND OF THE INVENTION AND PRIOR ART

- The present invention refers to a use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to  
15 ~~an individual of a human being or an animal.~~<sup>3</sup> The invention also refers to a method for prophylactic or therapeutic treatment of obstructive lung diseases ~~of in individual of a human being~~<sup>5</sup> or ~~an~~ animal.<sup>5</sup>

- 20 Pulmonary emphysema is a common disease, which in particular affects smokers. The disease is characterised by a permanent expansion and destruction of the finest bronchi and the walls of the alveoli. Pulmonary emphysema is a very serious disease and the destruction process is irreversible so that the disease leads to  
25 increasing respiratory difficulties.

- Pulmonary emphysema belongs to a group of diseases usually called obstructive lung diseases due to the fact that the disease obstructs the flow in the respiratory tracts. The obstruction is the  
30 underlying cause also to pulmonary barotrauma, including spontaneous pneumothorax. These diseases have symptoms and localised effects to the lung tissue similar to pulmonary emphysema.

- 35 During normal inhalation the bronchi are expanded, which counteracts the obstruction to a certain extent. During the following exhalation the lung tissue is compressed, including the bronchi, and

(Marked-up version)

*greater the pressure*

a somewhat smaller gas volume may therefore flow through the respiratory tract. This leads to a valve effect when a certain balance arises. By a certain overpressure in the respiratory tracts and the lung, the obstruction may be overcome and the inhaled gas volume be emptied. The pressure in the lung is however not sufficient for completely emptying the lung. There is always a certain amount of air (residual volume; normally about 500 ml of an adult) in the lung after the first breath. This balance depends inter alia on and is influenced by the ambient air pressure; the more the weaker the respiratory tracts, especially for early born, immature children.

*Resulting in* During smoking the mucous membrane in the respiratory tracts and bronchi is irritated, which leads to a swelling of the mucous membrane. This swelling decreases the lumen of the respiratory tracts, i.e. the obstruction arises and thus the air flow in the respiratory tracts is restrained. This leads to an increase of the so-called valve effect, to a higher pressure in the respiratory tracts and the lung, and to a larger residual volume in the lung. The increase also leads to a destruction of tissue, which further reduces the gas exchange, i.e. the breathing capacity. If nicotine or nicotine-like substances are supplied, not via the respiration, a vessel contracting, decongestant effect, which reduces the obstruction, is obtained.

*above-described* *bron* *caused*  
25 Pulmonary barotrauma appears ~~due to such a~~ tissue destruction by the inner pressure. Pulmonary barotrauma may principally refer to one single alveolus or a smallest respiratory tract, or several small alveoli within the lung. If this tissue destruction process is expanded to the whole lung it is called pulmonary emphysema. In the cases  
30 when air is collected diffusely in the lung tissue proper, we have an interstitial emphysema or in a delimited way, a bulla (blister). If the air is collected adjacent to the pleura in a delimited manner we have a subpleural bleb. The air may also come to the intrapulmonary space and we have a so-called pneumomediastinum  
35 or into the heart sack; pneumopericardium. If the tissue destruction is expanded so that the pleura is destroyed, we have a spontaneous pneumothorax (SP). With regard to the fact that

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*remaining part of the*

pathophysiological changes in the lung are documented in case of SP, it is not any longer relevant to call SP a disease of the pleura.

*in the**or part of a*

- 5 The obstruction leads to an expansion in ~~a lung part~~ and thus to a compression of the surrounding lung ~~part~~. Such an expansion and compression is irreversible for a smoker even if he would stop smoking. If the surrounding compressed lung part is very large, surgery could be considered for removing a large significant blister and thus create space for the respiratory work. However, it is very
- 10 rare that a patient is suitable for such an operation, whereby an expected effect is far from being optimal.

- 15 The destruction of tissue may be localised to the upper part of the lung, due to bronchial anomaly at spontaneous pneumothorax or to the lower part of the lung at alfa-1-antitrypsin AAT-deficiency. AAT is an enzyme protecting the elastic fibres of the lung. The fibres are subjected to the largest load in the lower part, where the largest expansion of the lung takes place when we breathe. If the protecting effect ceases, the elasticity is lost and this can be easily
- 20 seen on the most stressed tissue part.

The destruction may also be general without anomaly or AAT-deficiency due to smoking.

- 25 Bilateral bronchial anomaly is an anatomical congenital obstruction with a characteristically changed branching structure of the respiratory tracts and this obstruction may be increased by smoking. Bilateral bronchial anomaly may today be shown by diagnostic methods known per se, for instance by means of X-ray
- 30 pictures disclosing the bronchial structure of a patient. The respiratory tracts consist of bronchi, which from the main bronchus are divided to smaller and smaller bronchi. The first bronchus forms the bronchus of the first generation, the bronchi after the first division are called the bronchi of the second generation, after the
- 35 second division the bronchi of the third generation, etc. Bilateral bronchial anomaly means that the bronchi of the third generation are missing in an individual and are replaced by very characteristic,

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irregular narrowing connections. The air exchange to and especially from the alveoli will thus be hampered by this defect bronchial structure, which is identifiable.

## 5 SUMMARY OF THE INVENTION

The object of the present invention is to provide a means, which counteracts such obstructive lung diseases in a prophylactic or therapeutic manner.

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This object is obtained by the use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to ~~an individual of a human being or an animal~~ for the purpose of counteracting  
15 obstructive lung diseases in a prophylactic or therapeutic manner.

20

The applicant has realised that nicotine, if it is <sup>not</sup> supplied via the respiration, has an inhibitory effect on the development of respiratory tract obstruction followed by the irreversible substance loss, elasticity loss and expansion of the lung tissue, i.e. the negative effects arising from pulmonary emphysema, pulmonary barotrauma and spontaneous pneumothorax. By supplying nicotine to the body of the persons suffering ~~by~~ pulmonary emphysema, it is thus possible to prevent or ~~to~~ limit the development of the disease.  
25 Nicotine also ought to have a prophylactic effect, i.e. the origin of pulmonary emphysema of persons having a risk to be effected by this disease, for instance smokers, which have stopped smoking, may be prevented by the supply of nicotine, however not via the bronchi, respiratory organs.

30

The definition <sup>of</sup> at least one substance based on nicotine and/or a substance produced from said one substance is to be given a broad interpretation and in this definition are included substantially pure nicotine, nicotine compounds, nicotine related compounds, nicotine  
35 derivatives, intermediate metabolites of nicotine and/or nicotine compounds, degradation products from nicotine or nicotine compounds with completely or partly identical, similar effects.

(Marked up version)

According to a further embodiment of the invention, the use is intended for said individual, which has a congenital bilateral bronchial anomaly. As mentioned initially, the destruction of the lung tissue, due to smoking, may be general without anomaly or due to AAT-deficiency. The applicant has however realised that the risk of serious obstructions in the lungs, which leads to pulmonary barotrauma, such as spontaneous pneumothorax and pulmonary emphysema, is substantially higher for smokers having a congenital bilateral bronchial anomaly than for smokers not having such an anomaly. This risk ought to be in the order of 2000-3000 % higher for smokers with, than smokers without bilateral bronchial anomaly. The formed structure of a bilateral bronchial anomaly is associated with a different function, such as ventilation, perfusion, and a high sensibility for external factors, such as smoking.

The object is also obtained by a method for prophylactic or therapeutic treatment of obstructive lung diseases of an individual of a human being or an animal, wherein said individual is supplied with a nicotine-based substance.

## DESCRIPTION OF EMBODIMENTS OF THE INVENTION

Investigations have been made showing an inverted correlation between smoking habits of pregnant women and the risk of pulmonary barotrauma of the new-born children of the women. Thus, new-born children of smoking women have a lower predisposition to get pulmonary barotrauma than new-born children of women which are not smoking. Investigations also show that fetuses of women which smoke have nicotine in the blood. This inverted relation thus indicates that nicotine may counteract obstructive lung diseases.

It is known to use nicotine, i.e. 3-(1-methyl-2-pyrrolidyl) pyridine for smoking cessation, i.e. for reducing the abstinence complaints. The use now proposed according to the present invention may thus be regarded as a second medical indication. The medical effect mentioned above may be obtained for smokers which are smoking,

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New Nat'l Pat. Appln. Ser/Pat/TM No. .... File No. <u>6783-01 wous</u> Inventor Name(s) <u>R.</u> Atty/Secretary <u>BRM/ARR (3/1/02)</u>		Date Received: <u>10/070177</u> <u>MAR 18 2002</u>
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<input type="checkbox"/> Specification - # of pages ..... <input type="checkbox"/> Claims - # of pages ..... <input type="checkbox"/> Drawings - # of sheets ..... <input checked="" type="checkbox"/> Amendment <u>Preliminary w/ marked-up</u> <input type="checkbox"/> Issue Fee/Publication Fee ..... <input type="checkbox"/> English translation document <input checked="" type="checkbox"/> Marked up copy of specification/ <del>claims</del> <input type="checkbox"/> Clean copy of specification/claims <input type="checkbox"/> Dec/POA	<input checked="" type="checkbox"/> Transmittal letter <u>w/ Duplicate</u> <input checked="" type="checkbox"/> Check - \$ <u>520 - ck.</u> <input checked="" type="checkbox"/> IDS and PTO/SB/08A <u>1449</u> <input checked="" type="checkbox"/> Copies of IDS citations <input type="checkbox"/> Maintenance Fee <input type="checkbox"/> Extension of Time <input checked="" type="checkbox"/> <u>copy I.P.E.A.</u> <input checked="" type="checkbox"/> <u>2 sheets (8,9) Amended Sheets</u> <input type="checkbox"/> ..... <input type="checkbox"/> .....	

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